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David Ojeda, Virginie Le Rolle, Majid Harmouche, Agnès Drochon, Hervé Corbineau, et al.. Sensitivity Analysis and Parameter Estimation of a Coronary Circulation Model for Triple-Vessel Disease. IEEE Transactions on Biomedical Engineering, 2014, 61 (4), pp.1208 - 1219. 10.1109/TBME.2013.2296971 . hal-00961247v2

HAL Id: hal-00961247

<https://hal-univ-rennes1.archives-ouvertes.fr/hal-00961247v2>

Submitted on 20 Mar 2014

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Sensitivity Analysis and Parameter Estimation of a Coronary Circulation Model for Triple-Vessel Disease

David Ojeda*, Virginie Le Rolle, Majid Harmouche, Agnès Drochon,
Hervé Corbineau, Jean-Philippe Verhoye and Alfredo I. Hernández

Abstract—Mathematical models of the coronary circulation have been shown to provide useful information for the analysis of intra-coronary blood flow and pressure measurements acquired during coronary artery bypass graft (CABG) surgery. Although some efforts towards the patient-specific estimation of model parameters have been presented in this context, they are based on simplifying hypotheses about the collateral circulation and do not take advantage of the whole set of data acquired during CABG. In order to overcome these limitations, this paper presents an exhaustive parameter sensitivity analysis and a multiobjective patient-specific parameter estimation method, applied to a model of the coronary circulation of patients with triple vessel disease. The results of the sensitivity analysis highlighted the importance of capillary and collateral development. On the other hand, the estimation method was applied to intraoperative clinical data from ten patients obtained during CABG, which permitted to assess patient-specific collateral vessel situations. These approaches provide new insights regarding the heterogeneous configuration of the collateral circulation.

Index Terms—Coronary circulation, collateral vessels, sensitivity analysis, parameter estimation.

I. INTRODUCTION

Coronary artery disease (CAD) is the result of the accumulation of plaque in the coronary arteries and represents one of the leading causes of morbidity and mortality worldwide. Intra-coronary plaque accumulation may lead to stenoses, which are pathological narrowings in these blood vessels, reducing or completely interrupting blood flow. The myocardial tissue irrigated downstream from stenotic lesions will receive an insufficient blood supply, leading to myocardial ischemia or infarction. In the case of triple-vessel disease, the right coronary artery is completely occluded, while the left arteries present partial stenoses. The recommended guidelines for patients with complete stenoses (right coronary artery occlusion) suggest a treatment based either on coronary angioplasty or coronary artery bypass graft (CABG) surgery [1].

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A wide range of computational models of coronary circulatory dynamics has been proposed in the literature, at different levels of detail, with the aim of assisting the clinicians in the pre and intraoperative phases of these procedures [2]. A common approach is based on Windkessel models, which are lumped-parameter representations of blood flow and pressure dynamics, based on an electrical circuit analogy [3]. Other approaches range from pulse-wave models to detailed anatomically-based 3D flow models of the coronary tree [2]. Yet, lumped parameter models provide an abstraction that is easy to understand, uses few parameters, and provides a good compromise between computational cost and accuracy [2], [4].

Considering Windkessel models of the coronary circulation, Wang et al. [5] proposed a representation of the left coronary tree and its branches, while integrating the effect of stenoses on blood flow and the systolic flow drop that characterizes the coronary blood flow. Later, Pietrabissa et al. [6] extended this approach with revascularisations through coronary bypass grafts and applying an intra-myocardial pump model [7] to explain the systolic flow. However, none of these models consider the blood supply through collateral circulation, which is often present in patients with CAD.

Collateral circulation is a network of alternative, small diameter vessels that develop in order to perfuse areas affected by an occlusion. These vessels, which are present since birth, grow depending on different trigger factors such as increase of pressure gradient, ischemia, wall shear stress, among others [8], [9]. Although their impact on CAD is still controversial, clinical studies have shown a correlation between collateral circulation and myocardial sensitivity to ischemia [10], [9]. In fact, the collateral development has been shown to be an relevant factor on the recovery of the infarcted left ventricle after reperfusion [11] and it helps prevent left ventricular aneurysms [12]. Unfortunately, the collateral perfusion is difficult to assess directly [13], [14] and, consequently, collateral perfusion is still poorly understood [2].

Thus, collateral vessels should be included in a model willing to represent CAD. In this sense, previous works of our team proposed an extension of Pietrabissa's model, by integrating collateral circulation and the right coronary artery [15]. Also, an initial validation of the proposed model in the CAD context has been performed, by reproducing the mean blood flows and pressures obtained from clinical data [16]. However, this validation was based on the unrealistic assumption that all collateral vessels presented the same characteristics (i.e. with

the same model parameters), independently of the myocardial region they irrigate.

In this work, we build up on the above-mentioned model integrating collateral vessels [16], with an emphasis on the analysis of the effect of heterogeneous parameters on the collateral network. We propose an exhaustive sensitivity analysis of the model, followed by an advanced parameter-estimation method designed to provide a model-based, patient-specific estimation of the collateral development for patients suffering triple-vessel disease. The clinical objective of the proposed approach is to help with the assessment of the development and influence of the coronary collateral circulation, which may be useful for the clinicians for the followup and post-operative treatment choices.

The paper is structured as follows: in Section II the available data is presented, the coronary model is described, and the sensitivity analysis and parameter estimation methods used for the model analysis are explained. In Section III, the results of these methods are presented, analyzed and discussed from both model and physiological points of view, and conclude with Section IV, in which we present the future directions of our work.

II. MATERIALS AND METHODS

A. Clinical measurements

The clinical data used in this study was obtained during an off-pump coronary surgical procedure, thoroughly described in previous publications of our team [17]. Pre-operative data, already presented in previous publications [16], [18], include artery diameter reductions due to stenoses, estimated with bi-plane angiographies. Additionally, a visual estimation of collateral filling, presented in Table I, shows the Rentrop classification [19] of each patient (0: no observable filling due to collaterals, 1: observable filling of the distal branches without filling on the epicardial segment, 2: partial filling on the epicardial segment, and 3: complete filling due to collaterals). Intra-operative data consist of pressure and flow measurements, acquired at different places of the coronary tree during the revascularization surgery on ten patients with a chronic occlusion of the right coronary artery (RCA) and stenoses on the left main coronary artery (LMCA), left anterior descending (LAD) and left circumflex (LCx) (Figure 1).

During the CABG surgery, mean pressure and blood flow are measured under different graft configurations. First, the perfusion of RCA is reestablished with a saphenous vein graft (RCAg) from the aorta. At this moment, the graft is clamped while the aortic pressure (P_{ao}), central venous pressure (P_v) and pressure distal to the RCA occlusion (P_w) are measured (case 0G). Then, the graft is opened (case 1G) to measure P_{ao} , P_v , and the blood flow across the graft (Q_{RCAg}). Afterwards, the left coronary arteries are revascularized with two internal thoracic artery grafts (LADg and LCxg) from the aorta to the LAD and LCx. The same variables are measured with the right graft clamped (case 2G), but including also the blood flow across the left grafts (Q_{LCxg} and Q_{LADg}). Finally, when all the grafts are in place and opened, all measurements are repeated (case 3G).

TABLE I

PRE-OPERATIVE DATA OBTAINED FOR TEN PATIENTS WITH TRIPLE VESSEL DISEASE: PERCENTAGE OF AREA REDUCTION OF STENOSED ARTERIES AND RENTROP GRADE (0–3) OF THE RIGHT CORONARY ARTERY. STENOSIS DATA EXTRACTED FROM [16]. RENTROP EVALUATION EXTRACTED FROM [18].

Patient	LMCA (%)	LAD (%)	LCx (%)	Rentrop grade
1	26	99	90	3
2	46	89	95	2
3	92	85	96	3
4	19	86	97	3
5	20	88	92	3
6	85	94	82	2
7	80	0	85	3
8	87	70	90	1
9	83	78	0	1
10	75	93	0	2

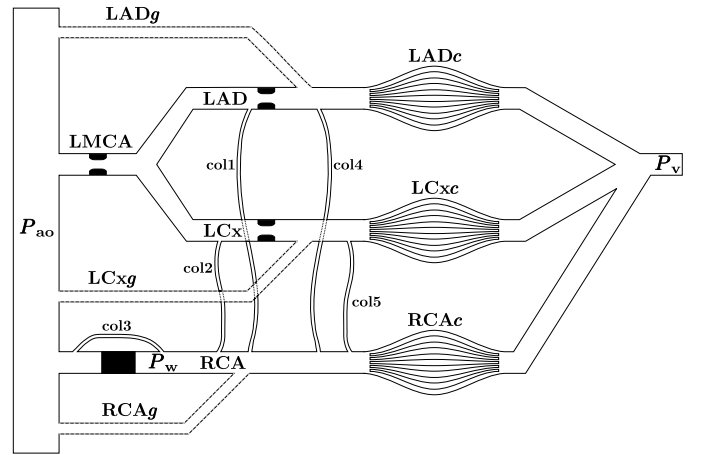


Fig. 1. Hemodynamic diagram of the coronary circulation of a patient with triple-vessel disease. A complete occlusion of the RCA is represented with a filled black box. Stenoses, represented with rounded black boxes, are present in the LMCA, LAD and LCx. Grafts implanted during the CABG surgery are represented with segmented lines.

Blood flow measurements were obtained using a transit time ultrasonic flow meter (Medistim Butterfly Flowmeter 2001). Blood pressure was acquired with a radial catheter. All available data are the mean value after hemodynamic stabilization, under the effect of glyceryl trinitrate, which induces vasodilation of large coronary arteries and arterioles.

B. Model description

As mentioned before, the model used in this work is directly based on the publication by Maasrani et al. [16], represented in Figure 2 and implemented using the M2SL simulation library [20]. In this model, each coronary artery is associated with an RLC circuit; the differential equations for these circuits can be found in [5]. Coronary arterioles and capillaries (LADc, RCAc, LCxc) and collateral vessels (col1, ..., col5) are represented by a lumped resistance, since resistive effects for these small diameters overwhelm the inertia and elasticity dynamics [4]. Collateral vessels are expected to exist in the five locations shown in Figure 1, a configuration that resembles a similar study in [21]. However, they can also be

undeveloped, which would be represented by a very high value of the collateral resistance. Parameter values related to arteries and grafts are extracted from previous works by Pietrabissa et al. [6], with adjustments according to the area reduction due to stenoses [5]; while parameters associated with small arteries will be identified from clinical data. Using the aortic (P_{ao}) and venous (P_v) pressure inputs, blood flows and pressures can be simulated across all arteries, capillaries, collaterals and grafts, including the total coronary flow (Q_t) as the sum of blood flows through all capillaries. Note that in this work, we refer to the lumped resistance of the coronary arteriolar networks as *capillary resistances*.

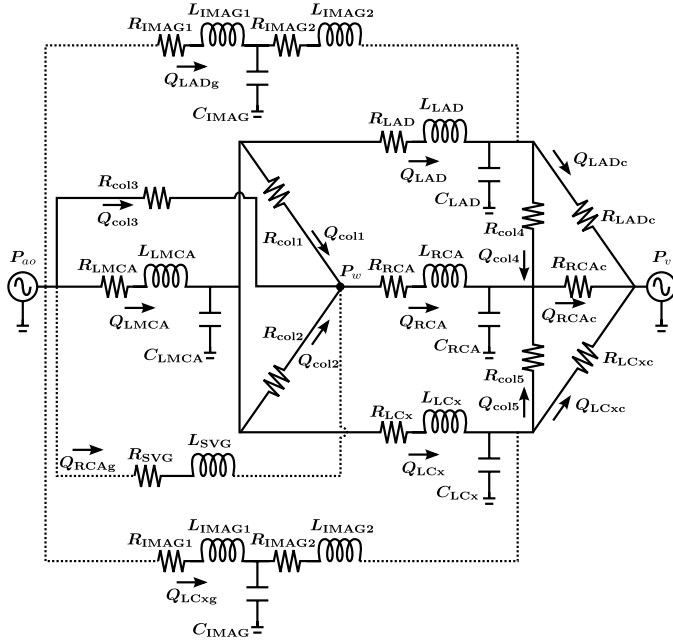


Fig. 2. Model of the coronary circulation.

One of the most important features of this model is the integration of the collateral vessels as resistances (R_{col}). Previous works were based on the assumption that all R_{col} are equal (homogeneous collateral development). However, recent clinical trials have shown that CAD patients present an heterogeneous collateral development [14], which depend on several factors, such as the vascularisation of the coronary circulation, development and severity of stenoses, duration of ischemic episodes, metabolic disorders, among others [10]. In this work, we study the effect of this heterogeneous collateral development through a sensitivity analysis of the model and propose a model-based method to estimate a patient-specific collateral development, eliminating the constraint of the equality of all R_{col} .

C. Sensitivity analysis

A parameter sensitivity analysis was performed on the coronary circulation model, in order to study, in particular, the relative sensitivity of the parameters on the main outputs of the model. Until today, sensitivity analyses have been applied locally only to a limited number of parameters [22], [23] and under the hypothesis of an equal collateral development. In this

paper, the screening method of Morris [24] was chosen because not only it permits to define a rank of the importance of each parameter, but it also provides information on non-linearities and interactions between parameters. Given a deterministic system f defined as:

$$\mathbf{y} = f(\mathbf{p}), \mathbf{y} \equiv (y_1, \dots, y_M), \mathbf{p} \equiv (p_1, \dots, p_N), \quad (1)$$

the Morris screening method estimates the sensitivity of each output y_i to each parameter p_j . This estimation consists on the evaluation of a set of *elementary effect* ($|EE_{ij}|$), defined as the change of variable y_i after a perturbation Δ of parameter p_j :

$$|EE_{ij}| = \frac{|f(p_1, \dots, p_j + \Delta, \dots, p_N) - f(\mathbf{p})|}{\Delta}. \quad (2)$$

The value of \mathbf{p} is randomly selected from a space of interest ω : a regular N -dimensional k -level grid, such that each p_j takes a random value from $\{0, 1/(k-1), 2/(k-1), \dots, 1 - \Delta\}$. The calculation of random $|EE_{ij}|$ is performed for r repetitions. From these r samples, the mean and standard deviation ($\mu_{ij}^* \pm \sigma_{ij}$) can be calculated. A large μ_{ij}^* shows a significant sensitivity of output i to parameter j , whereas large σ_{ij} are associated with non-linear effects or strong interactions of parameter j with other parameters. In order to establish a global sensitivity rank, one can calculate the Euclidean distance in the $\mu^* - \sigma$ plane, from the origin to each $(\mu_{ij}^*, \sigma_{ij})$ point:

$$S_{ij} = \sqrt{(\mu_{ij}^*)^2 + \sigma_{ij}^2}. \quad (3)$$

With this sensitivity index, which has been widely used in other modeling applications [25], [26], parameters with high sensitivity or strong interactions will have a high S_{ij} . In this paper, the analysis of S_{ij} will be used to evaluate the relative sensitivity of the collateral vessel parameters with respect to the other parameters of the model, and for the most important output variables.

In the interest of using physiologically relevant parameter values during the sensitivity analysis, the ranges for each parameter were defined as follows. Aortic and venous input pressures are simulated as pulsatile signals, adjusted to have a mean value between 60 to 120 mmHg for P_{ao} , and 3 to 14 mmHg for P_v . Capillary resistances were limited to the ranges shown in Table II. These ranges were arbitrarily defined by taking the mean values published by Maasrani et al. [16], which were estimated from patient data, and multiplying it by 0.2 and 3.85 in order to create a range that is large enough to contain all patient-specific values used for this model until today in [15], [16], [23]. Parameters related to arteries and grafts (R , L and C) were defined similarly, taking the baseline values shown on Table II, which were estimated from angiographic measurements in [5], [6], and multiplying by the same factors. The observed outputs were the mean values of blood flows and pressures during six cardiac cycles.

D. Parameter identification

Determination of important parameters with the sensitivity analysis provides key information towards accurate simulations and patient-specific parameters. Previous works attempting the

TABLE II

BASELINE PARAMETER VALUES FOR VESSELS OF THE CORONARY MODEL AND RANGES FOR SENSITIVITY ANALYSIS (IN BRACKETS).

Vessel	Resistance (mmHg s/mL)	Inductance (10 ⁻¹ mmHg s ² /mL)	Capacitance (10 ⁻³ mL/mmHg)
LMCA	0.1 [0.02, 0.39]	0.2 [0.04, 0.77]	2.0 [0.40, 7.70]
LAD	0.5 [0.10, 1.93]	0.3 [0.06, 1.16]	1.5 [0.30, 5.78]
LCx	0.3 [0.06, 1.16]	0.2 [0.04, 0.77]	1.1 [0.22, 4.26]
RCA	0.3 [0.06, 1.16]	0.2 [0.04, 0.77]	0.8 [0.16, 3.08]
IMAGI	1.4 [0.28, 5.39]	0.8 [0.16, 3.08]	5.4 [1.08, 20.79]
IMAGII	5.3 [1.06, 20.41]	1.7 [0.34, 6.55]	–
SVG	0.2 [0.04, 0.77]	0.4 [0.08, 1.54]	–
Capillaries	[27, 525]	–	–
Collaterals	[104, 2000]	–	–

creation of personalized models of the coronary circulation in CAD, focus on the calculation of capillary and collateral resistances, assuming that collateral resistances are represented by a common parameter for each patient. This approach, presented by Maasrani et al. [15], considers the measured graft flows for the 2G and 3G graft scenarios. Capillary resistances are calculated analytically under the 3G case since the left and right pressures are similar and the collateral flows are negligible; collaterals are estimated numerically in the 2G case, using the difference between the simulated and measured P_w .

In this work, we propose a parameter identification procedure that, on the contrary, seeks to estimate these collateral resistances individually, in a patient-specific manner. The proposed parameter estimation method will focus on the most sensitive parameters of the model, which have been determined by the rank of importance calculated during the sensitivity analysis phase.

In order to obtain an estimation that is as close as possible to real data, all the clinical measurements, under all graft scenarios, are compared to simulated data. The estimation is defined as the joint minimization of the following functions:

$$f_V(\mathbf{p}) = |V^{\text{cli}} - V^{\text{s}}|$$

$$\text{for all } V \in \{P_{w,0G}, Q_{\text{RCag},1G}, P_{w,2G}, Q_{\text{LADg},2G}, Q_{\text{LCxg},2G}, Q_{\text{RCag},3G}, Q_{\text{LADg},3G}, Q_{\text{LCxg},3G}\}, \quad (4)$$

where $^{\text{cli}}$ denotes variables observed during the CABG procedure for a particular patient and $^{\text{s}}$ denotes the corresponding variables simulated by the model using the parameter vector \mathbf{p} . Here, both simulated and observed variables are the average value after hemodynamic stabilization and not their continuous, pulsatile values.

Since the error functions defined in Equation (4) are not differentiable with respect to the model parameters, an evolutionary algorithm (EA) will be used to estimate the

model parameters. EAs use mechanisms inspired by natural evolution, such as selection, crossover and mutation, in order to generate solutions to optimization problems. In this family of algorithms, an *individual* is a representation of a possible solution to the optimization function, i.e. a parameter value set \mathbf{p} (note that, in this work, we use the term *individual* only to refer to the EA representation of a solution, and not to a *patient*). In general, EAs follow a common pattern, which starts with the initialization of a population of random individuals; each parameter value of \mathbf{p} of the individual is randomly set, bounded to a specified space. Next, each individual is evaluated, using an objective function, in order to calculate its *fitness*: a measure that directly impacts the ability of the individual to survive and combine with others to generate new solutions. Then, the population is repetitively evolved for a number of generations, using the following procedure: 1) selection of parent individuals for combination, which is biased towards the ones that have the best fitness, 2) combination of parent individuals, according to a probability p_c , which performs a crossover operation that generates two new child individuals. Then, with a probability p_m , these individuals are modified through a mutation operation, 3) re-evaluation of new individuals, 4) replacement of individuals in the population, usually by elimination of the less-fit individuals. Each particular procedure of the EA can be implemented differently, creating a variety of algorithms within the EA family, applicable to a wide diversity of problems. More details on these algorithms and operators are available in [27].

Considering our approach for the parameter estimation of the coronary model, which aims to minimize all eight functions in Equation (4), a multiobjective evolutionary algorithm (MOEAs) is more appropriate. They have been designed to find individuals that minimize conflicting objective functions; a feature also known as pareto-efficiency [28]. This means that the individuals found by these algorithms cannot reduce any further the value of any objective function without increasing another one.

In our particular case, the parameter estimation of the coronary model, the nondominated sorting-based multiobjective evolutionary algorithm (NSGA-II) [28] was selected to perform the optimization. This choice was based on the following key features of NSGA-II: (i) pareto estimation through domination: the fitness of individuals is defined according to their dominance; an individual dominates another one when it can minimize one or more objective functions without increasing another one, (ii) elitism: the replacement procedure keeps the best, dominant individuals, throughout the evolutive process, and (iii) diversity preservation: the selection process favors the individuals that are different from each other, which encourages the exploration of the parameter space and avoids local minima.

In order to avoid populations with dominant individuals that have nonetheless high error values for some of their objective functions, an additional consideration was included: Whenever the population contains 95% of dominant individuals, the mean of the sum of all objective functions of Equation (4) is calculated. Then, the evolutive algorithm is resumed with an additional constraint that penalizes any individual whose sum of objectives is greater than the mean. With this modification,

individuals with high global error are systematically replaced with others that minimize the sum of objectives.

III. RESULTS AND DISCUSSION

A. Sensitivity analysis

The sensitivity analysis was performed with different levels $p = 10$ and 20 , and number of repetitions $r = 100, 200, 500$ and 1000 , all which produced similar results. This convergence of the results showed that the number of repetitions was sufficient, providing the requirements to assess the ranking of the parameters with confidence. Here, we present the results for $p = 20$, $\Delta = p/(2(p-1)) = 0.526$, and $r = 1000$. Results are organized by output and graft scenario, sorted by their S_{ij} as defined in Equation (3). Figure 3 shows coronary blood flow through all arteries and total coronary flow, Figure 4 shows flows through collateral vessels, and Figure 5 shows flows through graft vessels and blood pressure distal to the RCA occlusion.

1) *Common sensitivity patterns and most sensitive parameters:* Regarding the identification of the most sensitive parameters of the model, the results reveal some common patterns for all outputs. There is a significant sensitivity to the resistive effects of the vessels, and a very low effect from inertances and capacitances. This is caused by the use of averaged output variables throughout several cardiac cycles, even though the simulation uses pulsatile signals for P_{ao} and P_v . When averaging output variables, phase dynamics are filtered out. Considering that all clinical data related to this study are average values after hemodynamic stabilization, all previous studies, including this work, continue to use mean values of the model output.

Another pattern of the results is that capillary resistances present the most important effect. As shown in Figures 3 and 5, all arterial and graft flows exhibit this behavior. Artery flows present an outstanding effect from capillaries, with a sensitivity at least ten times higher than the next parameter in the rank. The collateral flows results in Figure 4 are the only outputs where this pattern is less pronounced, since the sensitivity of the capillaries is similar to that of the resistance of the associated collateral vessel. These observations show that capillary resistances are an important regulator of coronary blood flow, which is a known fact, supported by clinical studies that acknowledge the importance of arterioles and capillaries on the regulation of myocardial perfusion [29]. Moreover, it has also been identified that collateral resistances influence the myocardial blood flow [30]. Results of the sensitivity analysis also agree with this clinical observation, considering that myocardial blood flow is related to the variable Q_t of the model. Furthermore, it is possible with the model to compare the effect of both mechanisms: a perturbation of capillary resistances provokes a more important change in Q_t than a similar perturbation of any collateral resistance.

2) *Role of the right capillary bed:* The presence of capillary resistances as important parameters for each output is consistent with the analog electrical network of Figure 2; each arterial and graft flow depends on the most distal resistance of the respective branch. However, the capillary for the right circulation R_{RCAc}

presents systematically a high sensitivity rank, even for blood flows of the left circulation, such as Q_{LMCA} , Q_{LAD} and Q_{LCx} , under the 0G and 2G cases. This effect of R_{RCAc} on the left circulation is only possible through the collateral flow between right and left coronary branches.

The right capillary bed is also a major determinant of all collateral flows, as shown in Figure 4. No other capillary resistance seems to have an important effect for the hemodynamics of the collateral network. This result is closely related to the sensitivity results for P_w in Figure 5. In this coronary model, collateral flows are directly proportional to the pressure difference between the left and right coronary branches (i.e. the pressure gradient between P_{LMCA} , P_{LAD} or P_{LCx} , and P_w). Consequently, any modification of P_w should have a similar effect on collateral flows.

The sensitivity analysis suggest that there is a different role of the right and left capillary beds on the coronary circulation due to collateral flow. To our knowledge, there is no clinical study that addresses this observation. However, this is coherent in triple-vessel disease, where the left beds are affected by partial stenosis, while the right bed could be damaged by the RCA thrombosis. It is worth mentioning that the model does not consider distal collaterals between LCx and LAD, which could result in a more significant contribution of the left capillaries.

3) *Uneven effect of collateral resistances:* Since one of the objectives of this work is to revise the hypothesis of the equality of collateral resistances, we examined closely the effect of these parameters on all model outputs. First, it is clear from Figure 4 that collateral resistances are the most important parameters for the collateral blood flow. Each Q_{col} depends primarily on their respective R_{col} , yet the other resistances seem to have an effect as well, since they have an effect on P_w . This observation implies that incorrectly estimating any one collateral resistance will have a major effect on the corresponding vessel, and a non-negligible effect in the whole assessment of the collateral situation of the patient.

Regarding the effect on other model outputs, for cases 0G and 2G it seems that collaterals are also important parameters, but for Q_t and Q_{LMCA} there is no clear distinction between them. On the other hand, Q_{RCA} seems to be more affected by collaterals that originate in the proximal part of the circulation (R_{col1} , R_{col2} and R_{col3}) with respect to collaterals from more distal parts (R_{col4} and R_{col5}). The former collaterals have a flow directly proportional to P_{ao} or P_{LMCA} , while the latter are proportional to P_{LAD} and P_{LCx} . Due to the coronary tree structure, and particularly to the presence of partial stenoses in the left branches, flows Q_{col1} , Q_{col2} and Q_{col3} will have a higher driving pressure than Q_{col4} and Q_{col5} . The inequality of the sensitivities to collateral resistances could thus be caused by these differences of driving pressures.

A similar uneven effect of collaterals is also noticeable for Q_{LAD} and Q_{LCx} flows. Here, a modification of R_{col4} and R_{col5} provokes a more important modification of these flows since these collaterals directly steal blood flow from the LAD and LCx arteries in order to reperfuse the occluded RCA. As with Q_{col} flows, imprecise estimation of R_{col} will then have a perceptible effect on the mean blood flow of the

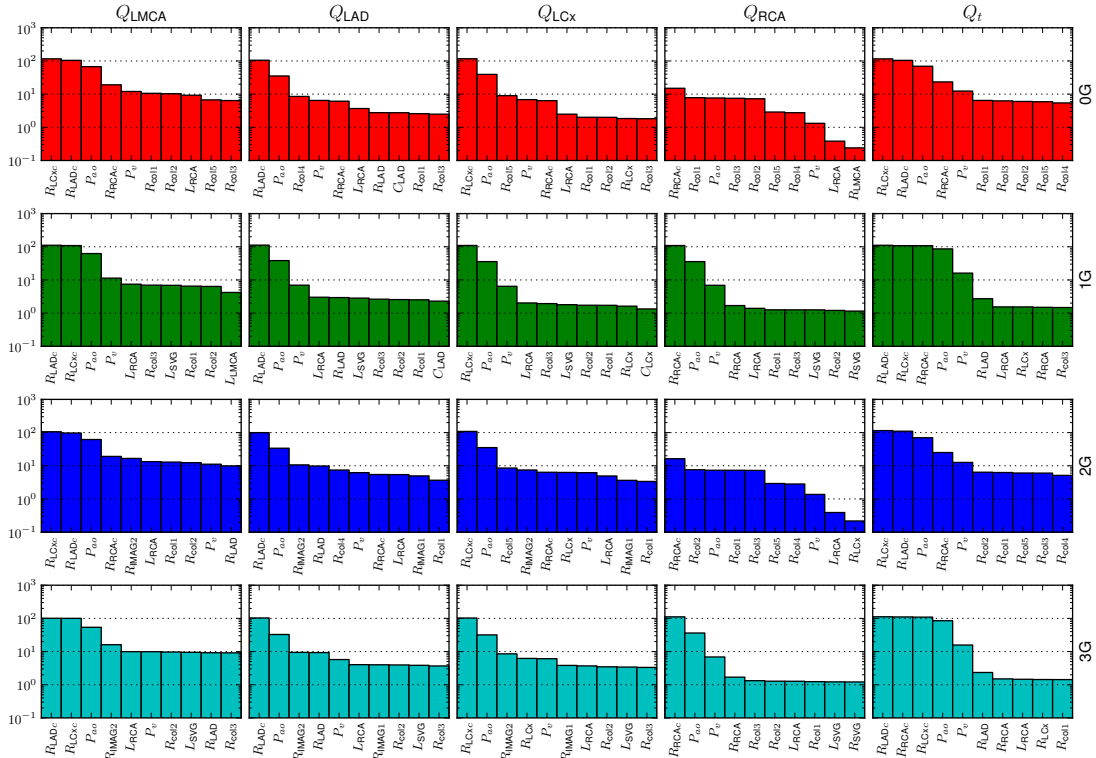


Fig. 3. Morris sensitivity results for the arterial flows (Q_{LMCA} , Q_{LAD} , Q_{LCX} , Q_{RCA}) and total coronary flow (Q_t). The Morris parameters used were $p = 20$, $\Delta = p/2(p-1) = 0.526$ and $r = 1000$ repetitions. Graphs are organized by graft cases (rows) and output variable (columns). Each graph contains only the ten most important parameters, where a bar represents the value S_{ij} as defined in Equation (3) (the higher the bar, the higher the influence of the parameter).

coronary arteries. Proximal collaterals will affect the right coronary hemodynamics, while distal will mostly affect the left counterpart.

4) *Effect of graft configuration:* The graft configuration deeply affects the sensitivity of the model parameters on all levels. Collateral resistances, which are usually among the most important parameters for arterial and collateral flows, become almost negligible under the 1G and 3G cases. As previously observed by [15], revascularization through the right graft reduces the pressure difference between the right and left branches of the coronary tree, hence the reperfusion through collateral vessels is reduced. Although significantly diminished, collateral flow is still present, since P_w results in Figure 5 show that this right territory pressure is still slightly sensitive to changes in the capillaries of the left territory and proximal collaterals.

In addition to the modification of the collateral dynamics, the presence of the right graft also increases the sensitivity of the right capillary, as shown for the results of Q_t , when comparing cases 0G and 2G with cases 1G and 3G. Since the right circulation is so poorly perfused due to the RCA occlusion (cases 0G and 2G), changes in R_{RCAc} do not produce an absolute effect as high as the changes in R_{LADc} or R_{LCXc} . With the presence of the right graft (cases 1G and 3G), the effective flow through RCA is higher, which re-enables the effect of the RCA capillary.

On the other hand, the presence of the LADg and LCXg (case 2G) does not have a major impact on the model outputs:

collateral vessels have the same effect as in the 0G case, and the right capillary sensitivity does not change for any variable. While these two grafts reperfuse the left territory, RCA is still poorly perfused due to its occlusion. Therefore, under this graft configuration, the right territory can only be reperfused through the collateral vessels, which explains why the R_{col} parameters are still observed as highly sensitive parameters.

5) *Effect of input variables:* Aortic pressure is consistently present in all arterial, collateral and graft flows. With respect to the model parameters, results show that, in general, P_{ao} is slightly less influent than capillary resistances, but more important than collateral resistances. On the other hand, P_v presents an effect that is comparable to the effect of collateral resistances. For all flows, with the exception of RCA, the effect P_{ao} and P_v does not show any significant variation among different graft cases. However, the presence of the right graft (cases 1G and 3G) increases the importance of P_{ao} and P_v on the Q_{RCA} , since the new graft flow directly depends on the pressure gradient between P_w and P_{ao} .

B. Parameter identification

Based on the sensitivity analysis results, which indicated that the most sensitive parameters for the coronary circulation model in a non-pulsatile configuration are the capillary and collateral resistances, the identification method was focused on estimating the optimal values for $\mathbf{p} = [R_{LADc}, R_{RCAc}, R_{RCAc-1G}, R_{LCXc}, R_{col1}, R_{col3}, R_{col4}, R_{col5}]$, where $R_{RCAc-1G}$ is the right capillary resistance for the 1G

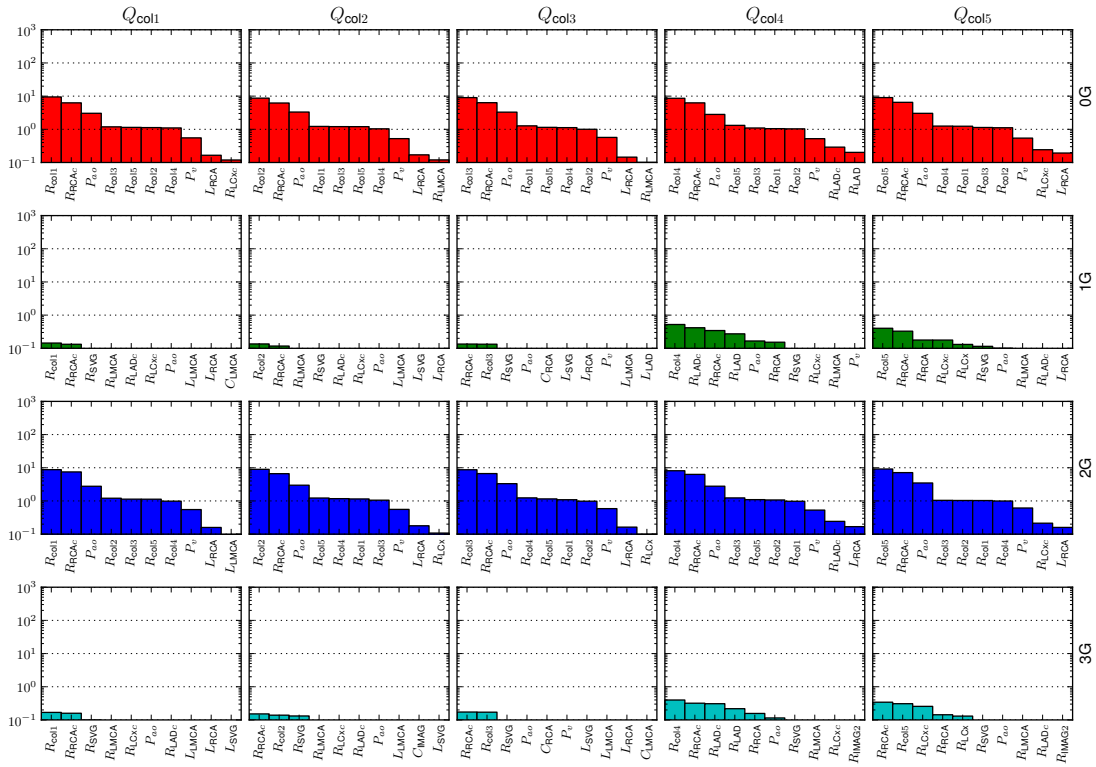


Fig. 4. Morris sensitivity results for the collateral flows (Q_{col1} , Q_{col2} , Q_{col3} , Q_{col4} , Q_{col5}). See Figure 3 for details on the sensitivity analysis parameters.

case. R_{col2} was not included in \mathbf{p} , but considered to be equal to R_{col1} . This is because these two resistances are in parallel (see Figure 2); several configurations of these resistances are equivalent, which would cause a high variability in the results. Each parameter was limited to the same physiologically plausible ranges used in the sensitivity analysis.

The MOEA optimization was run for each of the ten patients presented in [16], with a population for the evolutionary algorithm of 10000 individuals, during 500 generations, with a probability of crossover and mutation of $p_m = 0.8$ and $p_c = 0.25$, respectively. Results of the parameter estimation for each patient are shown in Table III. Different configurations with larger population sizes, more generations and different probabilities were also tested, generating similar results. Since the final population contains 10000 individuals, this table shows the mean value and the variability of the parameter values found in the 10% of the population with the lowest sum of the functions defined in Equation (4). Detailed information regarding the error for each objective function is shown in Table IV, as well as a comparison of the parameters found with the estimation procedure in [16].

1) *Evaluation of the estimation procedure:* The capillary resistances values found by the multiobjective estimation, shown in Table III, have a good consistency with the values of previous estimation by Maasrani et al., which are available at [16]. There are some exceptions: (1) patients 6, 8 and 9, with a difference in the R_{LADc} parameter of 128, 18.7 and 37.8 mmHg s/mL, respectively, and (2) patients 6, 8 and 10, with a difference in the R_{LCxc} parameter of 100, 53.3 and 45.2 mmHg s/mL, respectively. These differences are accounted

by the fact that the two estimation procedures are fundamentally different. Maasrani's estimation procedure, explained in [15] calculates R_{LADc} and R_{LCxc} by using the measured graft flow in the case 3G, while assuming a negligible collateral flow and constant collateral resistances. The sensitivity analysis results showed that these assumptions are not necessarily true.

Clinical data along with the estimated variables of the proposed method and previous publications are shown in Table IV; the table also shows the estimation error calculated with Equation (4). This evaluation measure shows a significant decrease in the total error for all patients. Patients 1 and 3 present the best improvements, with an error that is ten and twenty times lower. This major decrease is mostly due to the large difference with clinical data for the 1G case in previous identifications. In general, Maasrani's estimations have a significant error for this graft case. Since the Maasrani's estimation used only clinical data from cases 2G and 3G, it is not a surprise that simulations for cases 0G and 1G present a higher errors, while 2G and 3G variables are estimated more accurately. The proposed estimation method presents an improvement for almost all variables in all graft cases, because it exploits all available data for all cases. In particular, the Q_{RCAg} for case 1G always presents a lower estimation error. This improvement, as well as the close consistency with clinical data for Q_{RCAg} in the 3G case, is certainly due to the addition of a different R_{RCAc} for the 1G case. Finally, the low error on P_w variables for cases 0G and 2G improve the calculation of clinical indices based on this pressures, such as the pressure-based collateral flow index [31].

Patients 4, 5, 6 and 9 represent the estimation results

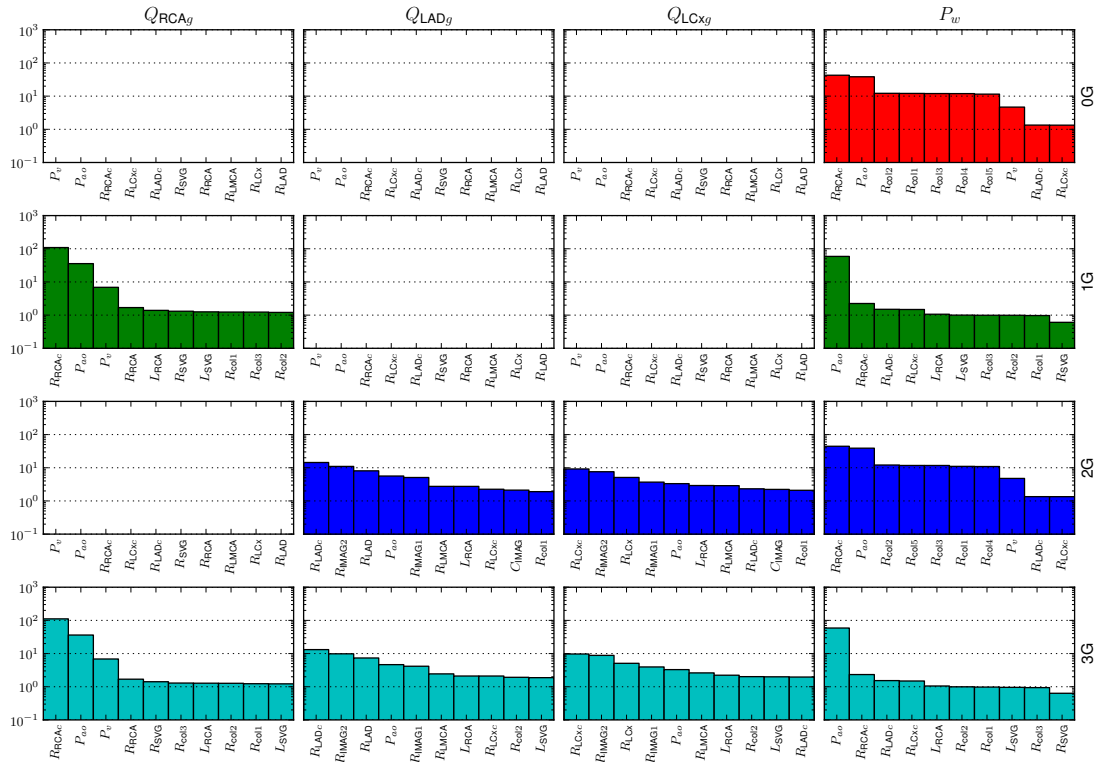


Fig. 5. Morris sensitivity results for the coronary graft flows (Q_{RCAg} , Q_{LADg} , Q_{LCxg}) and coronary wedge pressure (P_w). See Figure 3 for details on the sensitivity analysis parameters.

with the highest total error. However, they still improve the previous estimation by a significant difference. The source of the estimation error for these patients come mostly from the left graft flows and P_w . It can be noted in Table IV that whenever there is an important error in Q_{LADg} or Q_{LCxg} in the 2G case, there is no significant error in the 3G case. As with Q_{RCAg} , careful examination of the final population shows that individuals can either minimize $Q_{LADg,2G}$ or $Q_{LADg,3G}$, but not both at the same time, and similarly for Q_{LCxg} . Once again, introducing new R_{LADc} or R_{LCxc} for the particular case of 2G may improve the estimation error. Nevertheless, we decided not to include these additional parameters in order to keep the number of estimated parameters to a minimum.

2) *Modification of the right capillary resistance:* Concerning the right capillary resistance for the 1G case, Table III shows that there is an important modification of this part of the coronary circulation under that particular graft case. Excluding patient 9, the $R_{RCAc-1G}$ parameter shows a significant increase with respect to R_{RCAc} .

A possible scenario that could explain this increase of the right capillary resistance is the modification on the myocardial contractility of the right territory as a consequence of the reperfusion of this region. An improved contractility due to better oxygenation of the muscle would cause an augmented collapse of the capillaries. However, since the 3G case reperfuses in the same way the right territory, a similar effect was expected. This was not the case, since the estimation procedure showed that there is a strong relationship between the right capillary for the 1G and 3G cases.

3) *A new assessment of patient-specific collateral development:* Since the estimation procedure is not based on the equality of the collateral resistances, the results of Table III show an interesting way to estimate the collateral development in a patient-specific manner. These results can be compared with the Rentrop grade shown in Table III.

All ten patients included in this work show some collateral development (Rentrop grade higher than 0). This is consistent with the results obtained from the parameter identification phase, since all patients have at least one significantly low collateral resistance. In particular, patients 8 and 9, the only cases with a Rentrop grade of 1, present consistent results since they show high values (more than $1200 \text{ mmHg s mL}^{-1}$) for proximal collateral resistances. Patients 1, 3, 4, 5 and 7, whose Rentrop grade is 3, should show low resistances values (at most $350 \text{ mmHg s mL}^{-1}$) for one of the proximal collaterals and probably one of the distal resistances as well. Indeed, this pattern is true, except for patient 7, whose identified parameters show very high resistances (around or more than $1200 \text{ mmHg s mL}^{-1}$) for all collaterals but R_{col5} . The estimation error for this patient could be explained by the high error for P_w under the 0G case (Table IV) or by a misinterpretation during the evaluation of the Rentrop grade.

It should be noted that there is not always an agreement between the Rentrop grade and the parameter estimation results; the collateral assessment provided by this estimation cannot currently replace the Rentrop scoring system, but can be used as a complementary information that is not affected by intra or inter-observer errors. For instance, low values for collaterals

TABLE III

VALUES IDENTIFIED FOR TEN PATIENTS USING THE MULTIOBJECTIVE OPTIMIZATION METHOD. THE IDENTIFIED PARAMETERS WERE THE THREE CAPILLARY RESISTANCES (R_{LADC} , R_{RCAC} , R_{LCXC}), THE RIGHT CORONARY CAPILLARY FOR THE 1G REVASCULARIZATION CASE ($R_{RCAC-1G}$), AND THE COLLATERAL RESISTANCES ($R_{COL1} = R_{COL2}$, R_{COL3} , R_{COL4} , R_{COL5}). EACH ROW REPRESENTS THE $\mu \pm \sigma$ OF THE BEST 10% INDIVIDUALS IN THE FINAL POPULATION. R_{COL}^* IS THE COLLATERAL RESISTANCE ESTIMATED IN MAASRANI ET AL. [16]. RENTROP SCORE GRADES (RS) ARE INCLUDED FROM TABLE I FOR DISCUSSION IN TEXT. THE FINAL ROW SHOWS THE MEAN DIFFERENCE ACROSS ALL PATIENTS BETWEEN PARAMETER VALUES IN [16] AND THE VALUES FOUND BY THE MULTIOBJECTIVE ESTIMATION. ALL RESISTANCES VALUES ARE GIVEN IN mmHg s/mL.

Patient	RS	R_{LADC}	R_{RCAC}	$R_{RCAC-1G}$	R_{LCXC}	R_{col1}	R_{col3}	R_{col4}	R_{col5}	R_{col}^*
1	3	83.0±0.1	54.4±0.0	129.7±0.1	197.8±0.4	109.8± 0.2	1863.5±108.8	1974.8±24.8	104.0± 0.0	160
2	2	171.7±0.1	99.6±0.0	137.9±0.0	201.9±0.1	256.5± 6.8	1393.8±283.2	377.9± 1.7	104.1± 0.1	430
3	3	205.8±0.1	63.5±0.0	256.1±0.4	92.5±0.0	935.6± 25.5	104.2± 0.3	637.9± 8.3	344.6± 1.6	350
4	3	47.8±0.0	150.0±0.0	522.6±1.3	118.4±0.2	341.2±124.1	1212.9±442.4	897.8±11.1	1994.6± 7.3	565
5	3	169.8±0.1	58.7±0.0	95.0±0.0	65.1±0.0	104.8± 1.4	283.1± 15.8	104.1± 0.1	104.0± 0.0	205
6	2	368.1±1.0	117.7±0.0	203.8±0.1	234.6±0.8	1993.7± 7.1	245.6± 0.4	1998.3± 2.1	1995.8± 5.2	1055
7	3	53.8±0.1	77.6±0.0	82.0±0.0	106.6±0.0	1989.6± 14.8	1218.7± 30.4	1986.7±18.8	192.0± 0.3	650
8	1	58.8±0.2	357.1±0.1	523.9±0.1	248.7±0.6	1994.4± 8.3	415.4± 1.0	1990.9±10.7	1998.8± 1.8	970
9	1	337.4±0.4	84.9±0.0	59.9±0.0	27.8±0.0	1940.1± 57.5	1993.0± 9.1	286.7± 0.6	150.7± 0.8	420
10	2	152.6±0.2	215.5±0.1	324.0±0.5	106.7±0.9	1957.6± 40.1	112.5± 0.3	1364.8±24.5	1943.8±54.8	405
Difference with [16]		20.7	2.6	112.4	23.9	750.9	743.7	698.3	615.4	

R_{col4} and R_{col5} (well below 350 mmHg s mL⁻¹) were obtained for Patient 9, which can explain its Rentrop grade since these vessels reperfuse the RCA at the distal area. On the other hand, patient 8 showed values over 1800 mmHg s mL⁻¹ for these collaterals, which would not justify the distal collateral filling. Considering that the estimation results have a relatively low error for this patient, it is possible that this specific coronary circulation model is not appropriate for some patients. In particular, this model does not account for extracardiac collateral vessels, which can be found, although very rarely, on patients with triple-vessel disease [32].

Finally, identified parameters should be treated with care when the variability of the results is significant. As shown in Table III, the top 10% individuals of the final population for patients 1, 2 and 4 present a significant variability for R_{col3} ; one order of magnitude higher than all other variances. Patient 4 also shows this variation for R_{col1} . In consequence, we cannot affirm that R_{col3} (or R_{col1}) for these patients was successfully identified with the available data and the multiobjective procedure. Moreover, this significant variability has a small effect on the total error of the final population (Table IV), which indicates that these collaterals have a small sensitivity to the sum of functions in Equation (4). Although this seems to contradict the results of the sensitivity analysis, it only presents an interpretation of 1000 individuals with parameters in the restricted space defined around the mean and standard deviation shown in Table III; while the sensitivity analysis provided results on a much larger parameter space.

C. Limitations

The model and analyses presented in this work present some limitations that should be mentioned. First, our model represents the coronary circulation during the effect of vasodilators (glyceryl trinitrate) and anesthetics (propofol). In addition to partial vasodilation, particularly in larger arteries and arterioles with diameter > 100 μm [33], this attenuates coronary blood flow

autoregulation mechanisms of small arteries and arterioles, and the response of the autonomic nervous system. In consequence, parameter estimation results should be handled with care, since the resistances of coronary arteries and arterioles will increase under awake conditions. However, even in these conditions, the estimation of collateral development may not change significantly, since these vessels do not necessarily present smooth muscle.

As in our previous publications [15], [16], [18], we have represented the pressure loss across stenoses with a linear resistance, adjusted with respect to area reduction. This is a strong hypothesis that simplifies the simulation and identification phases and that allows us to compare the results of this paper with our previous works. However, this hypothesis is known to be unrealistic, since the stenosis resistance is dependent on flow [34], [35], [36]. Switching to a flow-dependent representation will lead to different estimated parameter values. Indeed, the driving pressure of proximal collateral vessels will drop, which affects the estimation of these resistances. However, the integration of a flow-dependent representation will not affect the main findings of this paper on the tendencies of parameter sensitivity and the analysis of the effects of heterogeneous collateral developments.

The model simulations and parameter estimations are currently based on generic geometric properties of the epicardial arteries and grafts, which generate the parameters of Table II. More precise estimations can be achieved using patient-specific measurements of these vessels, but clinical data used in this work does not include this information. Fortunately, the sensitivity analysis showed that these parameters present a lower effect compared to capillary and collateral resistances; the effect of assuming generic parameters for arteries and grafts should be minor.

Since clinical data do not include full flow profiles, all studies of this coronary model, including this one, consider the mean values of the model outputs, even if it is simulated with pulsatile values. Therefore, current results do not take

TABLE IV

SIMULATION RESULTS FOR THE CORONARY CIRCULATION MODEL: CLI^* VARIABLES ARE FROM CLINICAL DATA, $M1^\dagger$ ARE FROM SIMULATIONS OF MAASRANI ET AL. [16], $M2^\ddagger$ ARE FROM THE BEST SOLUTION FOUND BY THE MULTI-OBJECTIVE ESTIMATION. TOTAL ERROR WAS CALCULATED AS THE CUMULATIVE SUM OF FUNCTIONS IN EQUATION (4) FOR PRESSURE OR FLOW VARIABLES. ERROR FOR $M2^\ddagger$ IS THE MEAN AND STANDARD DEVIATION OF THE BEST 10% INDIVIDUALS OF THE FINAL POPULATION.

Case	Variable	Source	Patient									
			1	2	3	4	5	6	7	8	9	10
0G	P_w	cli*	35.0	49.0	40.0	43.0	53.0	35.0	29.0	46.0	37.0	47.0
		M1 [†]	31.6	44.5	33.1	38.3	41.4	28.2	37.0	45.1	37.9	44.9
		M2 [‡]	35.0	48.9	39.8	43.0	48.6	34.9	35.4	45.9	37.7	47.0
1G	Q_{RCAg}	cli*	35.0	45.0	28.0	11.0	63.0	18.0	53.0	9.0	60.0	11.0
		M1 [†]	88.2	52.4	86.6	35.1	85.4	31.9	55.9	14.6	45.6	18.9
		M2 [‡]	35.1	45.3	28.1	11.0	63.5	18.1	53.6	9.2	61.0	11.0
2G	P_w	cli*	31.0	49.0	40.0	42.0	36.0	28.0	40.0	43.0	40.0	48.0
		M1 [†]	31.3	49.0	40.1	42.3	35.7	28.4	40.2	44.5	40.0	48.2
		M2 [‡]	30.7	58.3	43.2	42.8	42.8	32.6	39.8	43.2	39.9	48.0
	Q_{LADg}	cli*	34.0	23.0	22.0	59.0	24.0	11.0	28.0	38.0	24.0	20.0
		M1 [†]	39.6	24.0	28.5	54.3	22.3	17.9	36.3	31.8	23.1	21.7
		M2 [‡]	34.9	23.1	22.1	54.7	24.1	11.0	28.4	38.3	24.4	20.1
	Q_{LCxg}	cli*	27.0	32.0	48.0	40.0	56.0	12.0	43.0	16.0	60.0	7.0
		M1 [†]	17.6	22.4	49.2	30.2	46.6	22.6	37.5	19.9	41.1	15.9
		M2 [‡]	20.8	29.8	48.2	28.5	49.0	12.0	43.2	16.1	42.2	7.0
3G	Q_{RCAg}	cli*	66.0	45.0	74.0	26.0	69.0	30.0	51.0	10.0	51.0	14.0
		M1 [†]	67.6	45.4	75.3	27.0	70.5	30.3	52.0	10.5	53.2	14.8
		M2 [‡]	66.5	45.3	74.6	26.0	69.8	30.2	51.4	10.0	51.6	14.0
	Q_{LADg}	cli*	40.0	21.0	19.0	57.0	18.0	14.0	28.0	28.0	23.0	18.0
		M1 [†]	38.9	21.1	19.0	56.8	18.3	14.3	28.2	28.1	22.9	18.0
		M2 [‡]	40.4	21.1	19.1	57.9	18.1	9.2	23.1	35.0	23.4	18.0
	Q_{LCxg}	cli*	14.0	19.0	45.0	30.0	46.0	18.0	29.0	17.0	45.0	13.0
		M1 [†]	13.9	19.2	44.7	30.1	45.6	18.1	29.2	17.2	44.6	13.0
		M2 [‡]	14.1	19.1	45.2	30.1	46.1	10.0	29.2	14.3	46.2	6.3
Variables		Source	Total error									
Pressures (mmHg)	M1 [†]	3.6	4.7	6.0	5.0	11.9	6.9	8.8	1.8	2.0	2.1	
	M2 [‡]	0.5±0.0	0.3±0.1	0.2±0.1	5.4±0.0	0.8±0.3	0.0±0.0	6.6±0.0	0.0±0.0	0.9±0.0	0.0±0.0	
Flows (mL/min)	M1 [†]	71.1	18.7	64.6	39.9	37.6	30.3	19.4	18.1	56.8	18.1	
	M2 [‡]	1.3±0.0	11.2±0.1	3.4±0.1	12.2±0.0	12.7±0.3	17.5±0.0	5.3±0.0	10.3±0.0	19.0±0.0	6.9±0.0	

into account the flow variations during diastole and systole that characterize coronary flow. Results should be considered relevant only when considering the mean values, but not phase dynamics, which explains the low effect of parameters related to capacitances and inductors. Similarly, parameters found during the estimation will correctly simulate mean clinical data under vasodilation, but not flow variations during the cardiac cycle.

IV. CONCLUSIONS

This paper presents two original contributions towards the improvement of a coronary circulation model, devoted to patients with triple-vessel disease undergoing CABG surgery. First, an extensive parameter sensitivity analysis was presented, where it was determined that the capillary resistances are the most important parameters, followed by the collateral resistances. The disparity of the effect of collateral resistances for some of the model output variables, particularly the blood flow on the RCA, emphasizes the importance of considering heterogeneous, patient specific representations of the collateral

circulation. Second, a multiobjective approach was proposed to estimate patient-specific parameters. This estimation is based on an original approach exploiting all available pre- and intra-operative data, without imposing any constraint regarding the parameters of the collateral vessels and considering a single parameter perturbation during the CABG. Results provide an estimation of the collateral and capillary development of a given patient, which may be a potentially useful marker for post-operative followup to CABG. Moreover, the estimated parameters showed an improvement with respect to an analytic approach [15] and previous (mono-objective) evolutive algorithm optimization methods [37]. However, a number of limitations persist in our model, as mentioned in Section III-C, that will be addressed in our future developments. Further work is thus directed towards: *i*) representation of flow-dependent resistances in arterial stenoses, *ii*) integration of coronary flow variations during the cardiac cycle, and *iii*) better estimation of patient-specific stenosis resistances through semi-automatic analysis of coronary CT images [38]. All this improvements

are facilitated by the multiobjective identification approach proposed in this work, which can be more easily generalized than our previous analytical approaches.

V. ACKNOWLEDGMENTS

This study was supported by Région Bretagne, France, who grants a research allocation (ARED) to the first author.

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